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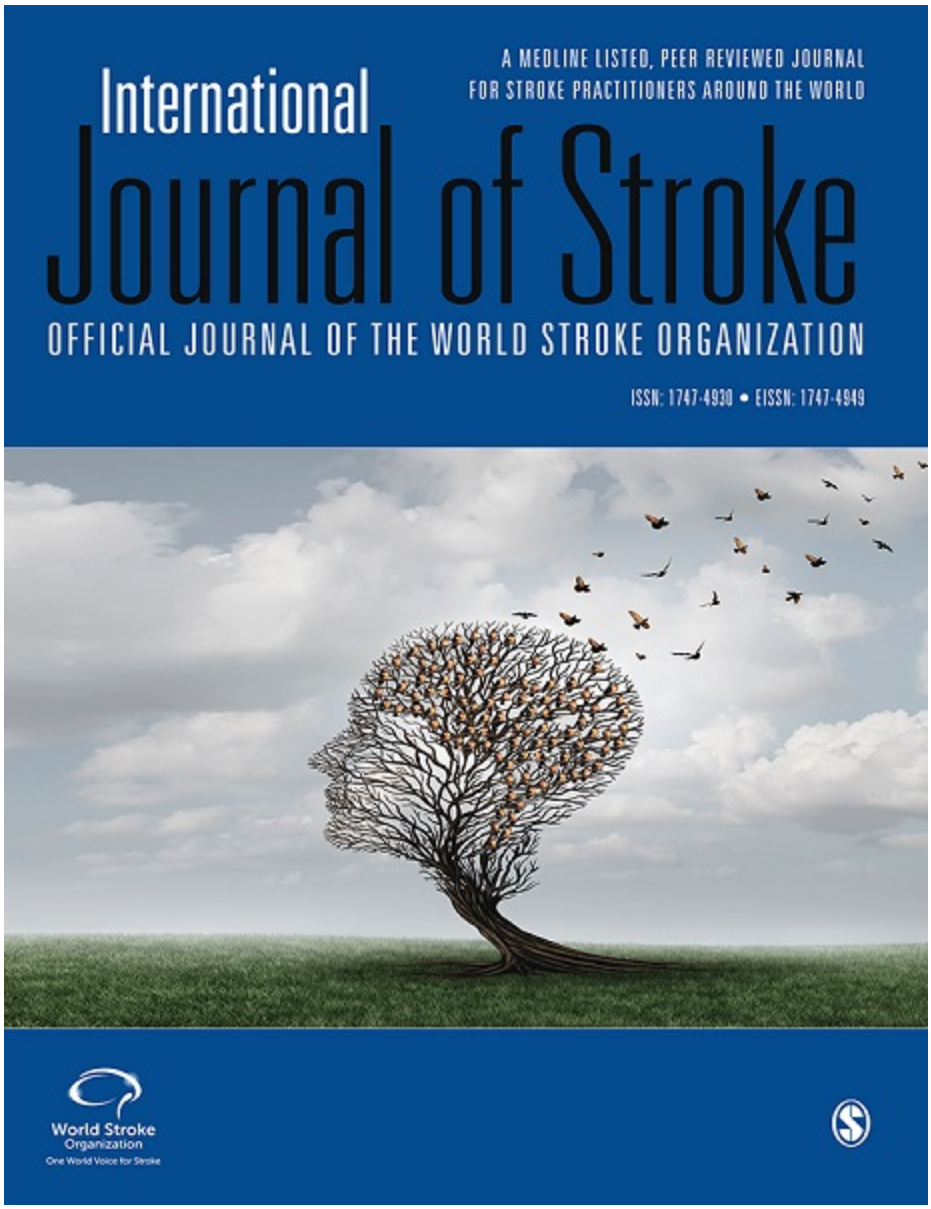

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Complete List of Authors:	Podlasek, Anna; NIHR Nottingham Biomedical Research Centre; Anglia Ruskin University, Neuroscience and Vascular Simulation Dhillon, Permesh; Nottingham University Hospitals NHS Trust, Interventional Neuroradiology; NIHR Nottingham Biomedical Research Centre Butt, Waleed; Nottingham University Hospitals NHS Trust, Interventional Neuroradiology Grunwald, Iris; University of Dundee School of Medicine, Division of Imaging Science and Technology; Anglia Ruskin University, Neuroscience and Vascular Simulation England, Tim; University of Nottingham School of Medicine, Stroke, Division of Mental Health and Clinical Neurosciences, ; University Hospitals of Derby and Burton NHS Foundation Trust, Stroke
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Direct mechanical thrombectomy without intravenous thrombolysis versus bridging therapy for acute ischaemic stroke: a meta-analysis of randomized controlled trials

Anna Podlasek[1,2*#], Permesh Singh Dhillon[1,3#], Waleed Butt[3], Iris Q Grunwald[2], Timothy J England[4,5]

1. NIHR Nottingham BRC, University of Nottingham, Nottingham, United Kingdom

2. Division of Imaging Science and Technology, School of Medicine, University of Dundee, Dundee, United Kingdom.

3. Interventional Neuroradiology, Queens Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom.

4. Stroke, Division of Mental Health and Clinical Neurosciences, School of Medicine, University of Nottingham, United Kingdom.

5. Stroke, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom

*Correspondence to: Anna Podlasek

Address: SPMIC, Derby Rd, NG7 2TP, Nottingham, UK

Email: podlasek.a@gmail.com

#Both authors contributed equally

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ABSTRACT

Background

Direct mechanical thrombectomy (dMT) may result in similar outcomes compared to a bridging approach with intravenous thrombolysis (IVT+MT) in acute ischaemic stroke. Recent randomised controlled trials (RCTs) have varied in their design and non-inferiority margin (NIM).

Aim

We sought to meta-analyse accumulated trial data to assess the difference and non-inferiority in clinical and procedural outcomes between dMT and bridging therapy.

Summary of review

We conducted a systematic review of electronic databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Random effects meta-analyses were conducted for the pooled data. The primary outcome was good functional outcome at 90 days (modified Rankin Scale (mRS)≤2). Secondary outcomes included excellent functional outcome (mRS≤1), mortality, any intracranial haemorrhage (ICH), symptomatic ICH, successful reperfusion (TICI≥2b) and procedure-related complications**.** Four RCTs comprising 1633 patients (817 dMT, 816 bridging therapy) were included. There were no statistical differences for the 90-day good functional outcome (OR=1.02, 95%CI 0.84-1.25, p=0.54, I^2=0%), and the absolute risk difference was 1% (95% CI −4% to 5%). The lower 95% CI falls within the strictest NIM of -10% among included RCTs. dMT reduced the odds of successful reperfusion (OR=0.76, 95%CI 0.60-0.97, p=0.03, I^2=0%) and any ICH (OR=0.65, 95%CI 0.49-0.86, p=0.003, I^2=38%). There was no difference in the remaining secondary outcomes. The risk of bias for all studies was low.

Conclusion

The combined trial data assessing dMT versus bridging therapy showed no difference in improving good functional outcome. The wide non-inferiority thresholds set by individual trials are in contrast with the clinical consensus on minimally important differences. However, our pooled analysis indicates non-inferiority of dMT with a 4% margin of confidence. The application of these findings is limited to patients presenting directly to MT-capable centres and real-world workflow times may differ against those achieved in a trial setting.

Introduction

Mechanical thrombectomy (MT) has become a standard of care for select acute ischaemic stroke (AIS) patients presenting with large vessel occlusion (LVO).[1,2] In the seminal trials comparing MT plus best medical therapy (BMT) versus BMT alone, intravenous thrombolysis (IVT) was administered in both arms when indicated.[2]

However, the efficacy of IVT in the setting of LVO is limited, with only 10% achieving successful reperfusion.[3] Additionally, the administration of bridging IVT before MT may incur a time penalty, lead to clot fragmentation and distal embolization, and increase the risk of symptomatic intracranial haemorrhage (sICH).[4–6] On the other hand, on-board IVT may lyse residual distal thrombi after MT and alter thrombus properties to facilitate endovascular removal[7]. These opposing factors have led investigators to question whether pre-treatment with IVT confers a net benefit.

Meta-analyses evaluating clinical and procedural outcomes following direct MT (dMT) versus a bridging IVT approach (MT+IVT) predominantly included observational and post-hoc studies and have yielded conflicting results.[8–11] Given the inherent selection biases in these investigations, the optimal reperfusion strategy remains unclear. Recently conducted randomized-controlled trials (RCT) have reported broadly similar outcomes for both approaches. The design of these trials varied such that three were powered to assess non-inferiority using different thresholds. Furthermore, results from two further ongoing multi-centre RCTs (SWIFT-DIRECT[12] and DIRECT SAFE[13]) are awaited. Hence, we undertook this systematic review and sought to meta-analyse consolidated data to test the null hypothesis that there is no difference in clinical and procedural outcomes following dMT compared to bridging therapy in AIS patients presenting with LVO.

Methods

Search Strategy, study selection and eligibility criteria

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was published in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (CRD42021233092). We systematically searched electronic databases up to January 2021, including PubMed/MEDLINE, Scopus, and Cochrane/EMBASE. Additionally, we included results presented during the International Stroke Conference (ISC) 2021. The following keywords were used in combination or individually by using the Boolean operators "OR" and "AND": randomi$ed, stroke, M1, MCA, large vessel occlusion$, isch$emic stroke, mechanical thrombectomy, endovascular therapy, direct thrombectomy, direct endovascular, thrombolysis, intravenous, tissue plasminogen activator, bridging thrombolysis, bridging therapy, alteplase, tenecteplase. The articles were selected in two stages. First, the titles and abstracts were screened for relevant studies and duplicates excluded. Second, the full texts were downloaded and assessed for eligibility. The reference lists of included publications were then hand-searched for additional relevant studies by three assessors with differences resolved by consensus (WB, PD, AP).

Only RCTs evaluating participants undergoing dMT versus bridging therapy with intravenous thrombolysis were included. The exclusion criteria included non-randomized controlled (retrospective and prospective) trials and pre-and post-intervention studies, observational and cohort studies or post-hoc analyses of RCTs, study protocols, review articles and meta-analyses, and studies that did not discriminate between dMT and bridging therapy.

Data Extraction

Variables recorded, if available, were the name of the first author, year of publication, study recruitment period, trial design, allocation type, primary end-point, stroke centre type, non-inferiority margin (NIM), sample size, onset to randomization time, randomization to alteplase time, randomization to groin time, mean age, number of males, presence of co-morbidities (namely hypertension, atrial fibrillation, diabetes, smoking, dyslipidaemia, prior stroke, prior cerebrovascular disease), prior medications (antiplatelets, anticoagulants), stroke aetiology (cardioembolic, large artery atherosclerosis, intracranial atherosclerosis, unknown/other), clot location (ICA, M1, M2, tandem occlusion), baseline National Institutes of Health Stroke Scale (NIHSS), and Alberta stroke program early CT score (ASPECTS), successful reperfusion rate (defined as extended or modified thrombolysis in cerebral infarction (TICI) scale of 2b or above), procedure related complications excellent functional outcome defined as modified Rankin score of 1 or lower (mRS≤1) at 90 days, good functional outcome defined as functional independence with a mRS≤2 at 90 days, sICH defined as any ICH with an increase of the NIHSS score of 4 or more within 24 hours or death, and ICH, and mortality at 90 days.

Outcome measures

The primary outcome was a good functional outcome (mRS≤2) at 90 days. The secondary clinical outcomes were excellent functional outcome (mRS≤1), mortality, sICH and any ICH. The secondary procedural outcomes included successful reperfusion (TICI≥2b) and procedure-related complications.

Statistical analysis

Study characteristics and extracted variables were summarized using standard descriptive statistics. Continuous variables were expressed as means and SD, and categorical variables were expressed as frequencies or percentages. Meta-analyses of binary outcomes were expressed as odds ratio (OR) with a 95%confidence interval (CI) and continuous variables as weighted mean difference (MD) with a 95%CI. A random-effects model and the Mantel-Haenszel method were used. Risk difference (RD) and OR random-effects meta-analysis to assess non-inferiority for the primary outcome (mRS ≤2 after 90 days).

Tests of heterogeneity were conducted with the Q statistic distributed as a chi-square variate (assumption of homogeneity of effect sizes). The extent of between-study heterogeneity was assessed with the I^2 statistic. Funnel plot and Egger's test were used to assess publication bias for the primary outcome. Rob-2 tool was used to evaluate and robvis tool to visualize the individual risk of bias of each study. P-values were two-tailed with values <0.05 considered statistically significant.

All analyses were implemented using JASP 0.14.1.0 and Review Manager 5.4.1.

Ethics

No human participant procedure was involved; therefore, informed consent and ethical approval were not essential for this study.

Results

Literature search results

We screened 838 non-duplicate titles and abstracts, from which 39 full-text articles were evaluated (Figure 1). Additionally, one study was identified during ISC 2021. Data was extracted from four studies. [14–17]

Studies Characteristics

We included four RCTs published between 2020-2021 describing 1633 patients (817 direct, 816 bridging) that underwent MT with or without iv-alteplase due to LVO in acute ischaemic stroke. The studies are summarised in Table 1. The detailed baseline characteristics are presented in Table 2.

Clinical outcomes

Bridging therapy and dMT were not associated with a difference in the odds of achieving good functional outcome (mRS≤2) at 90 days (Fig. 2; 4 studies; OR=1.02, 95%CI 0.84-1.25, p=0.64, I^2=0%). [14–17]. There was also no difference between groups in the excellent clinical outcome (mRs≤1) at 90 days (Fig. 3A; 4 studies; OR=1.08, 95%CI 0.86-1.36, p=0.71, I^2=0%), mortality at 90 days (Fig. 3B; 4 studies; OR=1.06, 95%CI 0.82-1.37, p=0.67, I^2=0%), or sICH (Fig. 3C; 4 studies; OR=0.82, 95%CI 0.55-1.21, p=0.31, I^2=0%). [14–17] The presence of any ICH occurred less frequently in the dMT group (27.8%) versus the bridging therapy group (36.3%) (Fig. 3D; 4 studies; OR=0.65, 95%CI 0.49-0.86, p=0.003, I^2=38%). [14–17]

Procedural Outcomes

Successful reperfusion (TICI≥2b) was achieved in significantly fewer participants in the dMT group (76.5%) versus the bridging therapy group (80.9%) (Fig. 4A; 4 studies; OR=0.76, 95%CI 0.60-0.97, p=0.03, I^2=0%).[14–17] This finding was mainly observed in two studies

including M2 occlusions (versus only ICA and M1 occlusions) (Fig. 4A, 2 studies, OR=0.75, 95%CI 0.57-0.97, p=0.03, I^2=0%)[14,17] There was no difference between groups in procedure-related complications (Fig. 4B; 2 studies; OR=0.83, 95%CI 0.49-1.40, p=0.49, I^2=56%). [14–17]

Risk of bias

All studies had an overall low risk of bias (Figure 5). Visual inspection of funnel plots did not reveal major asymmetry in studies that reported the primary outcome, though there are too few to reliably comment, and there was no statistical evidence of publication bias (Egger's test; z=0.95, p=0.343). [14–17]

Non-inferiority boundaries

The non-inferiority margin (NIM) for a good clinical outcome was 0.8 (OR) in DIRECT-MT and MR CLEAN NO-IV, 0.74 (OR) in SKIP, and -10% (RD) in DEVT. [14–17]

The RD in random-effects meta-analysis for the good clinical outcome was 1% (95% CI, −4% to 5%; p=0.64; I^2=0%). The lower 95% CI bound of −4% fell within the lead NIM of −10%, which was the strictest NIM among included RCTs.

The OR in random-effects meta-analysis for the good clinical outcome was 1.02 (95% CI, 0.84 to 1.25 p=0.83; I^2=0%, Figure 2). The lower 95%CI bound of 0.84 fell within the OR-NIM of 0.8.

Discussion

In this first systematic review and meta-analysis of RCTs comparing dMT versus bridging therapy, similar rates of good functional outcome (mRS≤2 at 90 days) were observed in both groups. Patients treated with dMT had significantly lower odds of successful reperfusion (TICI≥2b) and any ICH. However, there was no between-group statistical difference in the rates of excellent functional outcome (mRS≤1), mortality at 90 days, sICH, and procedural-related complications.

The absolute RD in the primary outcome of mRS≤2 at 90 days was 1% (95% CI −4% to 5%). Three of the included studies were powered to assess non-inferiority. In contrast to superiority trials designed to show that one treatment has greater efficacy than another, a non-inferiority trial is designed to show that a new treatment is not unacceptably worse than the current standard therapy. [18] Non-inferiority is claimed if the lower bound of the CI of the treatment effect difference does not exceed a pre-specified difference that is considered within acceptable boundaries based on statistical and clinical reasoning. Consensus recommendations are that the NIM is the smallest value that would be a clinically important effect.

Whilst there is no consensus on a non-inferiority meta-analysis methodology, we adopted the approach used where standard non-inferiority testing was applied to aggregated meta-analyzed outcomes. [19] A NIM can be chosen as an absolute RD or OR depending on statistical considerations such as event rates. [20,21]

The strictest NIM among the included RCTs was either 10% RD (DEVT) or 0.8 OR (DIRECT-MT and MR-CLEAN NO-IV). Their margins may be considered wide given that the minimally clinically important difference (MCID) is 1.5% to 5% as determined by stroke experts.[22] The lower 95% CI bound of −4% in our analysis fell within the NIM of −5%, however not within the more stringent NIM of −1.5%.[23]

There is an ongoing debate on the use of IVT before MT, proponents of which feel may favourably alter clot properties to facilitate removal, lyse distal thrombi and theoretically lead to higher first-pass effect rates and successful reperfusion. [24] However, it may also lead to clot fragmentation and render a patient ineligible for MT due to distal migration. On the other hand, dMT may allow faster door-to-groin-puncture times. However, none of the included trials showed a statistically or clinically significant reduction in the door-to-groin puncture time in the dMT group. The absence of IVT also potentially reduces the risk of peri-procedural haemorrhagic complications. Furthermore, there are direct and indirect cost implications of administering IVT, which requires a stroke physician's attendance and drug costs, thus favouring dMT as a first-line strategy.

Overall, our results suggest that IVT facilitates successful reperfusion (TICI≥2b), however, this does not translate to a significant difference in the good clinical outcome (mRS≤2 at 90 days). The limited efficacy of IVT before MT may be due to the relatively short duration of time from IVT administration to groin puncture that may have precluded the full therapeutic effect of IVT before the commencement of MT. Although not clearly evident in the included trials, a reason for the short duration from IVT-to-MT may be due to the delay in IVT administration in a trial setting, which involves recruitment, further imaging and randomisation processes, thereby distorting the real-world workflow. Moreover, in the included trials, all recruitment sites were MT-capable centres and hence the results only apply to patients presenting directly to such centres at a time when MT is immediately available.

Our sub-group analysis revealed that the two studies (DIRECT-MT and MR CLEAN NO-IV), which included M2 occlusions, had higher successful reperfusion rates (TICI≥2b) in the

bridging therapy group than the remaining two studies that only included ICA and M1 MCA occlusions (Figure 4A). This may be due to the lower efficacy of IVT in proximal occlusions.[25]

There have been multiple previous systematic reviews and meta-analyses of predominantly observational studies comparing dMT and bridging therapy, which have yielded conflicting results.[8,10] The most recent meta-analysis by Wang et al., which included 29 observational studies and one randomized trial (DIRECT-MT), concluded that better functional outcome (mRS≤2 at 90 days) was achieved with bridging therapy compared to dMT.[10] However, there was an overlap of some patient cohorts in the included studies, and most of the observational studies were inherent to selection bias (particularly in the dMT cohort, many of whom were ineligible for IVT treatment). Reasons for IVT ineligibility include a delayed presentation from stroke onset, which predisposes to a larger ischaemic core, especially in patients with poor collateral circulation, as well as prior use of anticoagulants, both of which could affect haemorrhagic complications and functional outcomes.

Furthermore, a subgroup analysis performed by Kaesmacher et al. of studies that only included patients eligible for IVT in the dMT cohort found no difference between both groups for the good functional outcome at 90 days, findings which are coherent with our analysis.[26] Our findings are also difficult to directly compare with prior analyses that included observational studies of both anterior and posterior circulation strokes and first-generation SR devices[27], which may have confounded the outcomes. Additionally, many retrospective studies did not report the outcomes of patients that received IVT but failed to proceed to MT due to clinical improvement and/or vessel reperfusion. All RCTs in our analysis used modern-day techniques and were deemed to have a low risk of bias and low heterogeneity.

Our analysis includes several limitations. First, the paucity of data on the outcomes according to the clot location, stroke aetiology (and correlating clot composition) or first-line MT techniques precluded sub-group analysis. Second, three of included studies were conducted in Asian populations, which limits generalizability of the findings to non-Asian populations. The remaining trials (SWIFT DIRECT and DIRECT SAFE) are expected to further inform this question. Third, there may be an inherent risk of bias in inclusion of the unpublished, non-peer-reviewed results from the MR CLEAN NO-IV study presented during the ISC 2021. Fourth, all analyses were only performed on an intention-to-treat basis; thus the definitive treatment may be different from the group allocated, which may have influenced the results. Fifth, the studies only included patients with anterior circulation strokes, so they cannot be extended to all patients with ischemic stroke. Sixth, only alteplase was used for IVT, which precludes comparisons to potentially more effective or safer thrombolytics, such as tenecteplase.[28] Finally, to fully understand the impact of treatment on clinical outcomes an ordinal shift mRS analysis should be performed on individual patient data.[29]

Conclusions

The combined trial data assessing dMT versus bridging therapy showed no difference in improving good functional outcome. The wide non-inferiority margins set by individual trials are in contrast with the clinical consensus on minimally important differences. However, our pooled analysis indicates non-inferiority of dMT with a 4% margin of confidence. The application of these findings is limited to patients presenting directly to MT-capable centres and real-world workflow times may differ against those achieved in a trial setting. The results of further ongoing multi-centre randomized trials are awaited.

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References

1. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. *Journal of NeuroInterventional Surgery*. Epub ahead of print 2019. DOI: 10.1136/neurintsurg-2018-014569.

2. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. Epub ahead of print 2018. DOI: 10.1161/STR.0000000000000158.

3. Tsivgoulis G, Katsanos AH, Schellinger PD, et al. Successful Reperfusion With Intravenous Thrombolysis Preceding Mechanical Thrombectomy in Large-Vessel Occlusions. *Stroke* 2018; 49: 232–235.

4. Kaesmacher XJ, Boeckh-Behrens T, Simon S, et al. Risk of thrombus fragmentation during endovascular stroke treatment. *Am J Neuroradiol*. Epub ahead of print 2017. DOI: 10.3174/ajnr.A5105.

5. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. Epub ahead of print 2014. DOI: 10.1016/S0140-6736(14)60584-5.

6. Bourcier R, Alexandre PL, Eugène F, et al. Is bridging therapy still required in stroke due to carotid artery terminus occlusions? *J Neurointerv Surg*. Epub ahead of print 2018. DOI: 10.1136/neurintsurg-2017-013398.

7. Desilles JP, Loyau S, Syvannarath V, et al. Alteplase Reduces Downstream Microvascular Thrombosis and Improves the Benefit of Large Artery Recanalization in Stroke. *Stroke*. Epub ahead of print 2015. DOI: 10.1161/STROKEAHA.115.010721.

8. Mistry EA, Mistry AM, Nakawah MO, et al. Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: A Meta-Analysis. *Stroke* 2017; 48: 2450–2456.

9. Kaesmacher J, Mordasini P, Arnold M, et al. Direct mechanical thrombectomy in tPA-ineligible and -eligible patients versus the bridging approach: a meta-analysis. *J Neurointerv Surg* 2019; 11: 20–27.

10. Wang Y, Wu X, Zhu C, et al. Bridging Thrombolysis Achieved Better Outcomes Than Direct Thrombectomy After Large Vessel Occlusion. *Stroke* 2021; 52: 356–365.

11. Phan K, Dmytriw AA, Maingard J, et al. Endovascular Thrombectomy Alone versus Combined with Intravenous Thrombolysis. *World Neurosurg* 2017; 108: 850-858.e2.

12. Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke - Full Text View - ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT03192332 (accessed 9 May 2021).

13. DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval - Full Text View - ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT03494920 (accessed 9 May 2021).

14. Yang P, Zhang YY, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020; 382: 1981–1993.

15. Zi W, Qiu Z, Li F, et al. Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke. *Jama* 2021; 325: 234.

16. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke. *Jama* 2021; 325: 244.

17. Roos Y, LeCouffe N, Kappelhof M, et al. Intravenous Thrombolysis Followed by Endovascular Thrombectomy versus Direct Endovascular Thrombectomy: A Randomized Controlled Trial. In: *International Stroke Conference, 18th March*. 2021.

18. Head SJ, Kaul S, Bogers AJJC, et al. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J* 2012; 33: 1318–1324.

19. Burgos AM, Saver JL. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. *Stroke* 2019; 50: 2156–2162.

20. Schumi J, Wittes JT. Through the looking glass: Understanding non-inferiority. *Trials*. Epub ahead of print 2011. DOI: 10.1186/1745-6215-12-106.

21. Kaul S, Diamond GA, Weintraub WS. Trials and tribulations of non-inferiority: The ximelagatran experience. *Journal of the American College of Cardiology* 2005; 46: 1986–1995.

22. Lin CJ, Saver JL. Noninferiority margins in trials of thrombectomy devices for acute ischemic stroke is the bar being set too low? *Stroke* 2019; 50: 3519–3526.

23. Cranston JS, Kaplan BC, Silver JL. Minimal clinically important difference for safe and simple novel acute ischemic stroke therapies. *Stroke* 2017; 48: 2946–2951.

24. Ohara T, Menon BK, Al-Ajlan FS, et al. Thrombus Migration and Fragmentation after Intravenous Alteplase Treatment: The INTERRSeCT Study. *Stroke* 2020; 203–212.

25. Seners P, Turc G, Maïer B, et al. Incidence and Predictors of Early Recanalization after Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. *Stroke* 2016; 47: 2409–2412.

26. Kaesmacher J, Kleine JF. Bridging Therapy with i. v. rtPA in MCA Occlusion Prior to Endovascular Thrombectomy: a Double-Edged Sword? *Clin Neuroradiol* 2018; 28: 81–89.

27. Phan K, Dmytriw AA, Lloyd D, et al. Direct endovascular thrombectomy and bridging strategies for acute ischemic stroke: A network meta-analysis. *J Neurointerv Surg* 2019; 11: 443–449.

28. Katsanos AH, Safouris A, Sarraj A, et al. Intravenous Thrombolysis with Tenecteplase in Patients with Large Vessel Occlusions: Systematic Review and Meta-Analysis. *Stroke* 2021; 308–312.

29. Podlasek A, Grunwald IQ, Musiałek P. The evolution from an "average" study patient to patient-specific characteristics to guide interventions in vascular medicine. *Polish Arch Intern Med* 2021; 131: 5–8.

Figure Legends

Fig. 1. PRISMA flowchart of the study selection process

Fig. 2. Forest plot of primary clinical outcomes: good clinical outcome at 90 days (modified Rankin Score, mRS≤2). Lines at OR=0.74/0.8 indicate the reported non-inferiority margins in the included trials.

Fig. 3. Forest plots of secondary clinical outcomes A. excellent clinical outcome at 90 days (modified Rankin Score, mR≤1), B. mortality at 90 days, C. symptomatic intracranial haemorrhage (sICH), D. any ICH

Fig. 4. Forest plots of procedural outcomes A. successful reperfusion defined as TICI≥2b with a subgroup analysis stratified according to the study inclusion criteria of the clot localization. B. procedure-related complications. ICA – internal carotid artery, M1 – M1 segment of the middle cerebral artery, M2 - M2 segment of the middle cerebral artery

Fig. 5. Risk of bias.

Tables

Study name	DEVT	DIRECT-MT	MR-CLEAN NO-IV	SKIP
Author, year	Zi, 2021	Yang, 2020	Roos, 2021	Suzuki, 2021
Study design	Non-inferiority	Non-inferiority	Superiority	Non-inferiority
Allocation method	RCT	RCT	RCT	RCT
Start to end of recruitment period	05/2018-05/2020	05/2018-05/2020	01/2018-10/2020	01/2017-06/2019
Sample size – direct MT vs Bridging therapy	116 vs 118	327 vs 329	273 vs 266	101 vs 103
Primary end-point	Good clinical outcome (mRS ≤2) at 90 days	Ordinal mRS	Ordinal mRS	Good clinical outcome (mRS ≤2) at 90 days
Non-inferiority margin	-10%	0.8	0.8	0.74
Alteplase dose	0.9 mg/kg	0.9 mg/kg	0.9 mg/kg	0.6 mg/kg
Time from onset to randomisation (dMT vs bridging, median, IQR)	N/A	167 (125-206) vs 177 (126-215)	94 (60-137) vs 93 (71-152)	N/A
Time from randomisation to alteplase (bridging, median, IQR)	7 (5-10)	7 (4-12)	98 (75-156)**	14 (10)*
Time from randomisation to groin puncture (dMT vs bridging, median, IQR)	32 (17-50) vs 34 (20-53)	31 (20-45) vs 36 (20-50.5)	130 (103-180)*** vs 135 (106-185)	20 (20)* vs 22 (16)
Stroke centre type	MT-capable	MT-capable	MT-capable	MT-capable
mRS≤2 at 90 days [dMT vs bridging, n/N (%)]	63/116 (54.3) vs 55/118 (46.6)	119/327 (36.4) vs 121/329 (36.8)	134/273 (49.1) vs 136/266 (51.1)	60/101 (59.4) vs 59/103 (57.3)

successful reperfusion (TICI≥2b) [dMT vs bridging, n/N (%)]	100/116 (86.2) vs 102/118 (86.4)	243/327 (74.3) vs 267/329 (81.2)	191/273 (70.0) vs 196/266 (73.7)	91/101 (90.1) vs 96/103 (93.2)
Risk of bias	Low	Low	Low	Low

Tab. 1. Study characteristics

dMT – Direct mechanical thrombectomy, mRS – modified Rankin score, RCT – randomized controlled trial, TICI – thrombolysis in cerebral infarction, OR – Odds ratio. IQR – interquartile range, N/A not available

* mean (SD), ** onset to alteplase, *** onset to groin,

Feature	Direct MT, n/N (%) or mean±SD/N	Bridging Therapy, n/N (%) or mean±SD/N
Socio-demographics		
Sample size	817	816
Gender (male)	471/817 (57.6)	463/816 (56.7)
Age (years)	70.2±12.1/817	69.5±11.8/816
Baseline characteristics		
NIHSS	16.3±7.0/817	16.6±6.7/816
ASPECTS	8.4±2.2/543	8.4±2.2/549
Co-morbidities		
HTN	323/544 (59.4)	336/550 (61.1)
DM	100/544 (18.4)	102/550 (18.5)
Dyslipidaemia	48/544 (8.8)	59/550 (10.7)
AF	357/817 (43.7)	338/816 (41.4)
Prior Stroke	69/544 (12.7)	80/550 (14.5)
Prior CVD	37/544 (6.8)	26/550 (4.7)
Smoking	70/217 (32.3)	83/221 (37.6)
Medications		
Antiplatelet	16/544 (2.9)	18/550 (3.3)
Anticoagulation	19/544 (3.5)	17/550 (3.1)
Clot Localization		
ICA	239/817 (29.3)	216/816 (26.5)
M1	449/817 (54.6)	541/816 (66.3)
M2	90/817 (11.0)	75/816 (9.2)
Tandem occlusion	34/544 (6.3)	42/550 (7.6)
Stroke Etiology		
Cardioembolic	278/544 (51.1)	285/550 (51.8)
Large Artery Atherosclerosis	87/544 (16)	72/550 (13.1)
Intracranial Atherosclerosis	54/443 (12.2)	42/447 (9.4)
Unknown/other	153/544 (28.1)	174/550 (31.6)

NIHSS=National Institutes of Health Stroke Scale, IV-tPA=intravenous tissue plasminogen activator, MT=mechanical thrombectomy, ASPECTS=Alberta stroke program early CT

score, HTN=hypertension, DM=diabetes mellitus, AF=atrial fibrillation, CVD=cardiovascular disease, ICA=internal carotid artery, M1=M1 segment of the middle cerebral artery, M2=M2 segment of the middle cerebral artery

Table 2: Baseline population characteristics

Figures

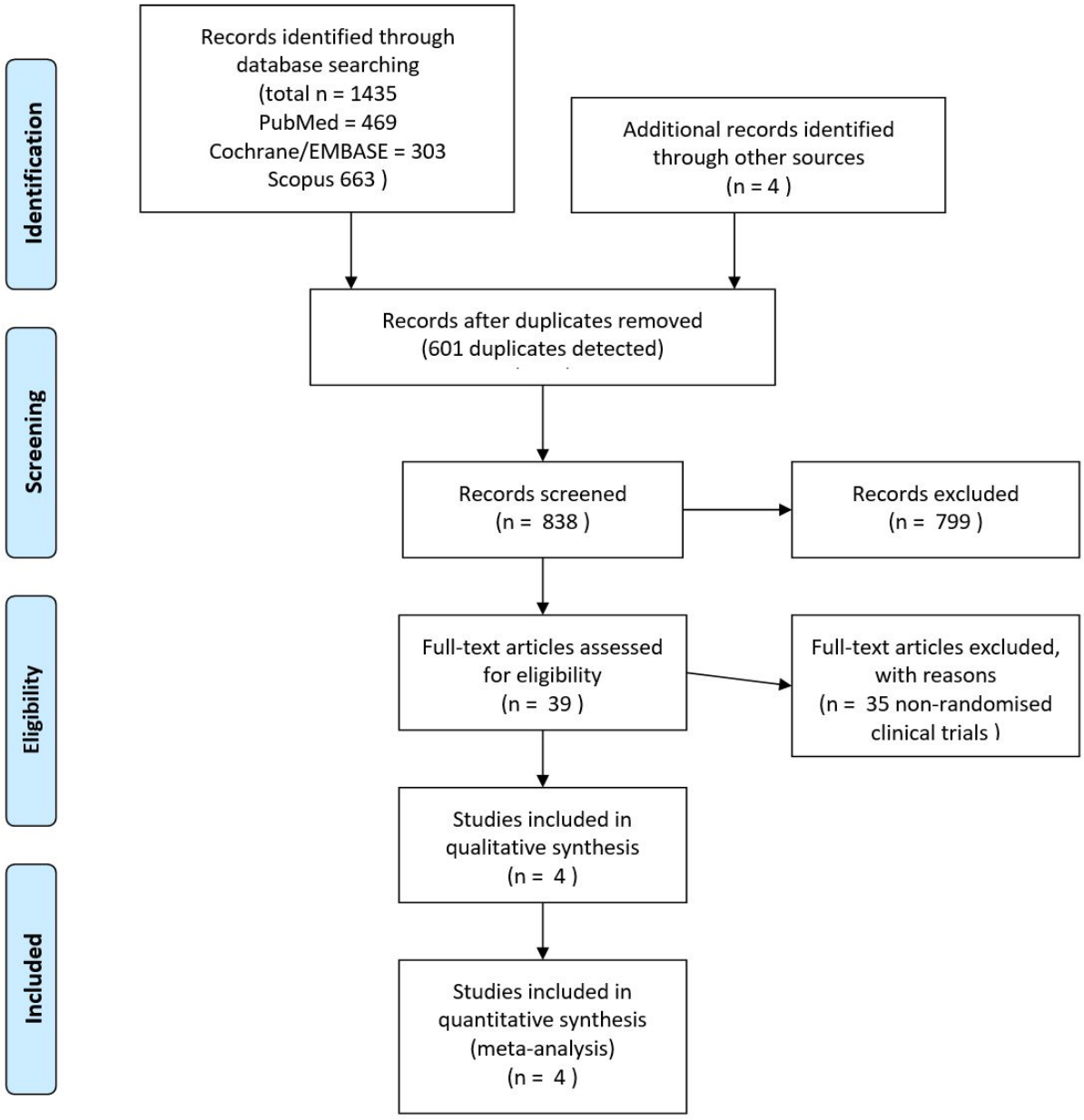

Fig. 1. PRISMA flowchart

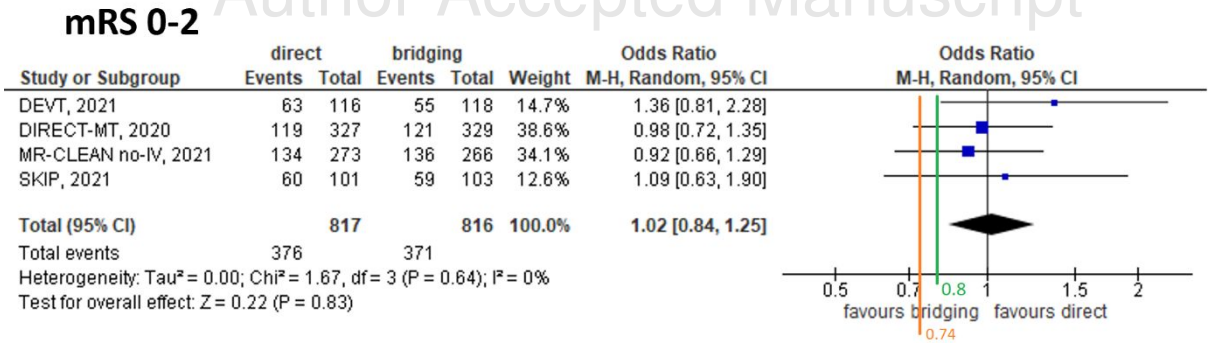

Fig. 2. Forest plot of primary clinical outcomes: good clinical outcome at 90 days (modified Rankin Score, mRS≤2). Lines at OR=0.74/0.8 indicate the reported non-inferiority margins in the included trials.

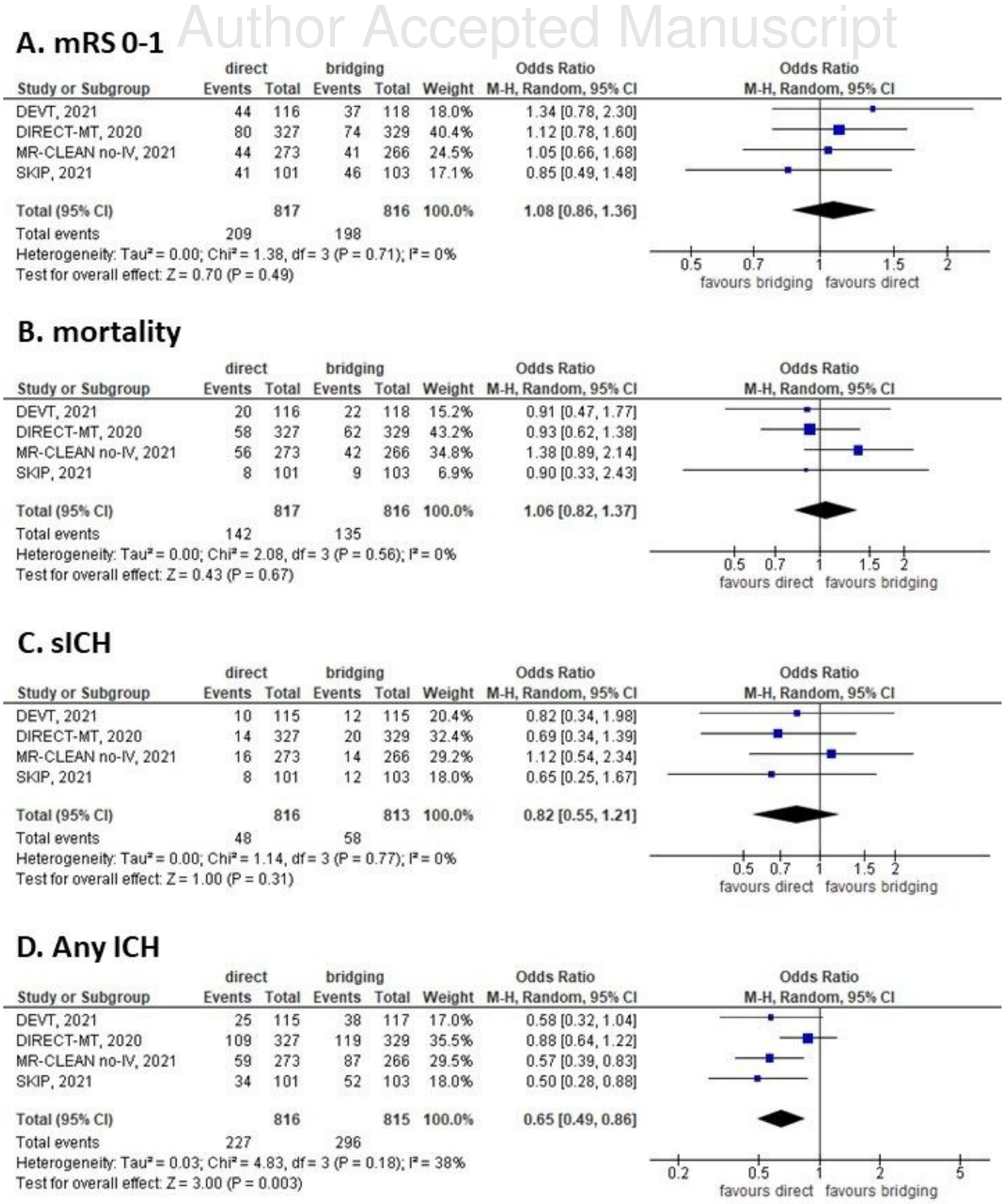

Fig. 3. Forest plots of secondary clinical outcomes A. excellent clinical outcome at 90 days (modified Rankin Score, mR≤1), B. mortality at 90 days, C. symptomatic intracranial haemorrhage (sICH), D. any ICH

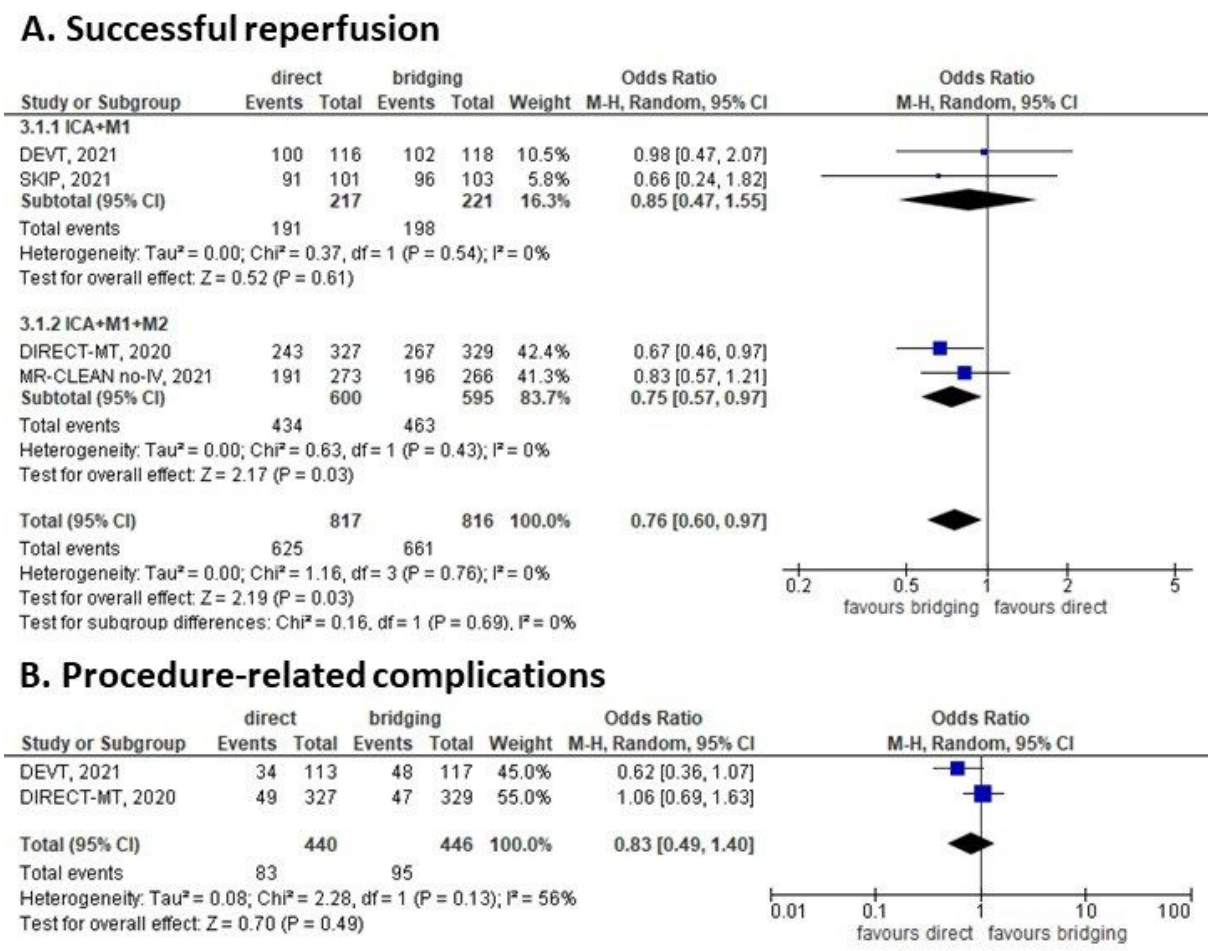

Fig. 4. Forest plots of procedural outcomes A. successful reperfusion defined as TICI≥2b with a subgroup analysis stratified according to the study inclusion criteria of the clot localization. B. procedure-related complications. ICA=internal carotid artery, M1=M1 segment of the middle cerebral artery, M2=M2 segment of the middle cerebral artery

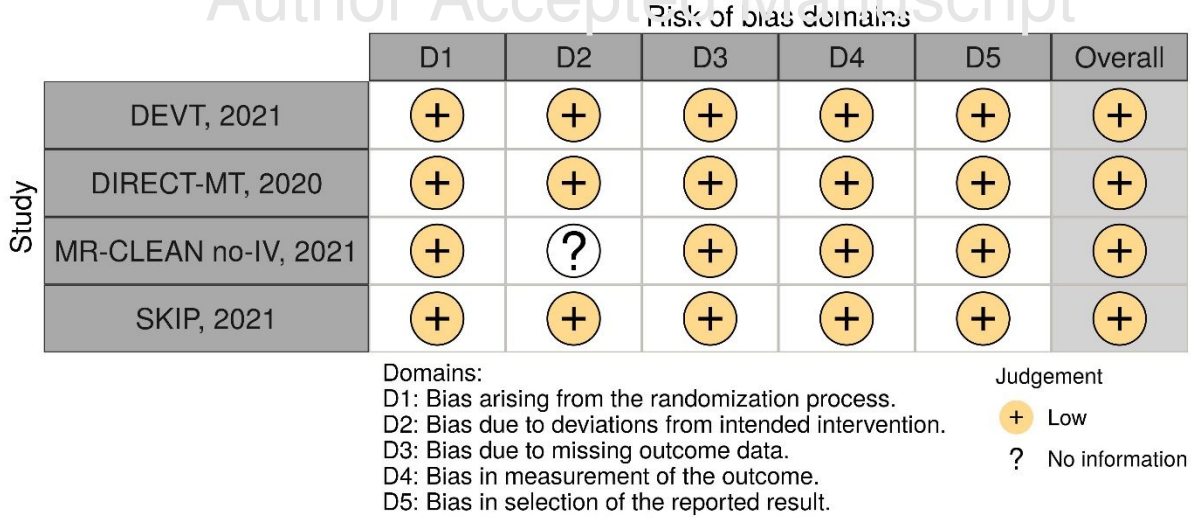

Fig. 5. Risk of bias